

10/519549

DT01 Rec'd PCT/PTC 28 DEC 2004

Process for the preparation of macrocyclic ketones by Dieckmann condensation in the gas phase

5 The present invention relates to a process for the preparation of macrocyclic ketones (C_{13} - C_{20}) by Dieckmann condensation in the gas phase over a heterogeneous catalyst. The process is used particularly in the production of fragrances, for example civetone and exaltonee, which are used widely in the perfume and
10 cosmetics industry.

The synthesis methods used hitherto are mostly based on a conventional intramolecular condensation reaction, such as the Dieckmann condensation in the liquid phase.

15

The synthesis of, for example, civetone by Dieckmann cyclization of 9-octadecene-1,18-dicarboxylic dialkyl esters and subsequent saponification and decarboxylation of the correspondingly obtained β -keto ester has been known for a long time (e.g.:

20 J. Tsuji, Tetrahedron Lett., 21, 2955-2958 (1980); Y. Choo, J. Am. Oil Chem. Soc. 71, 911-913 (1994)).

H.W. Bost (Perfumer & Flavorist, 1982, 7, 57) describes a reaction of a saturated diester in the gas phase over a thorium
25 oxide catalyst. However, the yields, at 14%, are markedly lower than in the customary cyclizations with high dilution.

The hitherto known methods for the preparation of macrocyclic ketones from linearly terminal diesters, however, have the
30 following serious disadvantages:

- 1) It is necessary to use a strong base in a stoichiometric amount.
- 2) In order to achieve good yields the reaction has to be
35 carried out with high dilution.
- 3) The β -keto ester which forms as an intermediate has to be saponified and decarboxylated in a separate step.
- 4) In the gas-phase reaction, extremely low yields are achieved. The catalyst used is expensive.

40

It is an object of the present invention to develop a preparation process for macrocyclic ketones which permits a simplified more economical mode of preparation.

45

We have found that this object is achieved according to the invention by a process for the preparation of macrocyclic ketones of the formula I

5

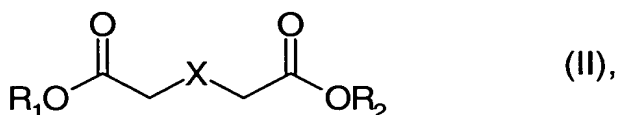


10 where

X is a mono- or polyunsaturated or saturated C₁₀-C₁₇-alkyl radical which may optionally be substituted by a C₁-C₆-alkyl radical,

15 by direct cyclization of compounds of the formula II

20



where

25 R₁, R₂, in each case independently of the other, may be identical or different and are hydrogen or C₁-C₆-alkyl and X has the meaning given above, in the gas phase over a heterogeneous catalyst.

30 In this process, the linearly terminal dicarboxylic acids, monoester monocarboxylic acids or the dialkyl esters of the formula II are evaporated and cyclized directly to give the ketone in the gas phase over heterogeneous catalysts.

35 A mono- or polyunsaturated or saturated C₁₀-C₁₇-alkyl radical is understood as meaning, for example, a

-(CH₂)₁₂-

-(CH₂)₁₄-

40 -CH(CH₃)-(CH₂)₁₁-

-CH=CH-(CH₂)₈-CH=CH-

-CH₂-CH₂-CH=CH-(CH₂)₆-CH=CH-CH₂-CH₂-

-(CH₂)₆-CH=CH-(CH₂)₆- or a

-CH₂-CH₂-CH=CH-(CH₂)₈-CH₂-CH=CH-CH₂- radical,

45 preferably a -(CH₂)₁₂- or a -(CH₂)₆-CH=CH-(CH₂)₆- radical.

3

A C₁-C₆-alkyl radical is understood as meaning, unless stated otherwise, a straight-chain or branched alkyl radical having 1 to 6 carbon atoms. Preference is given to the methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, pentyl or the hexyl group.

5

In a preferred embodiment, the fragrances exaltone (cyclopentadecanone) or civetone (cis-9-cycloheptadecen-1-one) are prepared by the process according to the invention.

- 10 The compounds of the formula II are prepared by methods known per se, as are described in the literature (e.g. JAOCs, Vol. 71, No. 8 (1994), pp. 911-913 or Tetrahedron Lett. Vol. 21, (1980), pp. 2955-2958)), under reaction conditions as are known and suitable for the synthesis. In this connection, use may also be made of
15 variants known per se which are not mentioned in more detail here.

The starting materials of the compounds of the formula II may, if desired, also be further reacted in situ without prior isolation
20 of the compounds of the formula II directly to give the compounds of the formula I.

- The advantage of the process according to the invention is that the cyclization, saponification and subsequent decarboxylation
25 steps which are normally customary in a Dieckmann condensation carried out in solution take place in a single step in the gas phase, without isolation of the respective intermediates. A further advantage is that less solvent is required, which leads to a cost advantage and a reduced amount of waste which may have
30 to be worked up.

The process can be carried out either in a fluidized bed or in a fixed bed. However, preference is given to carrying out the reaction in a fixed bed.

35

- The cyclization is carried out at temperatures of from 200 to 600°C, preferably 250 to 500°C. In principle, the reaction is possible under reduced pressure, at atmospheric pressure or under increased pressure. To make it easier to evaporate the
40 high-boiling starting materials, the reaction is preferably carried out under reduced pressure or at atmospheric pressure.

- The reaction may be carried out with the addition of small amounts of water in order, after the cyclization, to favor ester
45 hydrolysis steps. In this connection, the water can be added in one portion or in two or more steps at any desired point in the process, but before the mixture has completely passed the

catalyst (e.g. if II already comprises water or water is added in the evaporator).

Suitable catalysts for the process according to the invention are
5 all heterogeneous catalysts which comprise active components which are able to convert carboxylic acids, carboxylic esters or nitriles to ketones in the gas phase. Examples of such active components are oxides, hydroxides or carboxylates of subgroups I-VIII, or of main groups II, III and IV. Preference is given to
10 using oxides, hydroxides or carboxylates of subgroups I to VIII, particularly preferably those of subgroup IV. The catalysts are often also doped with further components (e.g. oxides of main group I) and can be used either as unsupported catalyst or as supported catalysts. Suitable support materials are materials
15 customary in catalyst chemistry, for example SiO_2 or Al_2O_3 .

It is particularly advantageous to use TiO_2 , in particular TiO_2 doped with alkali metal oxides or alkaline earth metal oxides, i.e. TiO_2 comprising about 2 to 10% by weight of Na_2O and/or K_2O .
20 The catalysts are prepared in accordance with the processes described in EP 352 674.

To carry out the process, the compound II in the form of a liquid or a melt or a solution in an inert organic solvent, for example
25 toluene or tetrahydrofuran is evaporated and then passed, optionally in the presence of an inert gas or mixtures of different inert gases, such as nitrogen, carbon dioxide or helium, at the desired reaction temperature in gaseous form over the catalyst arranged in a fixed manner or through a gas stream
30 of fluidized catalyst. In order, after the cyclization, to favor ester hydrolysis steps, the reaction can be carried out with the addition of small amounts of water. Preference is given to working with 0 to 30% by weight of water, preferably with 5 to 15% by weight of water, based on the amount of II used.

35 The reaction products are condensed using suitable cooling devices, or precipitated with a suitable solvent (quench) and then fractionally distilled. Reaction products containing unreacted starting material can optionally be returned again
40 directly to the cyclization reaction without further purification.

The process can be carried out continuously or as a batch process. Preference is, however, given to the continuous
45 procedure.

5

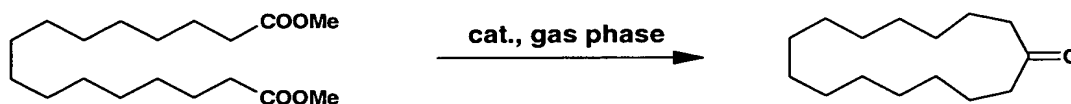
The process according to the invention requires no stoichiometric amount of strong bases, no solvents or other auxiliaries and directly produces the macrocyclic ketones in good yields and selectivities.

5

Examples

Example 1: Preparation of exaltonee from diethyl
1,16-hexadecanedioate

10



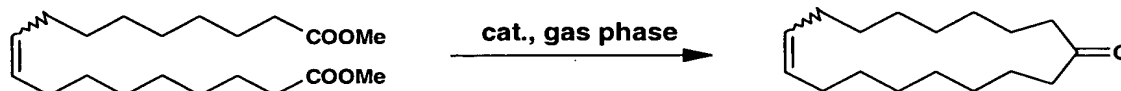
15

A solution of 10 g of diethyl 1,16-hexadecanedioate in 120 ml of tetrahydrofuran was evaporated in a gas-phase tubular reactor at 270°C and passed with nitrogen at 350°C over a catalyst ($\text{TiO}_2 + 2\% \text{K}_2\text{O}$). Condensation and fractional distillation were then carried out. The yield was 78% with a selectivity of > 90%.

20

Example 2: Preparation of civetone from dimethyl
1,18-octadec-9-enedicarboxylate

25



A solution of dimethyl 1,18-octadec-9-enedicarboxylate in toluene in a volume ratio of 1:9 was saturated with water until phase separation just no longer occurred. This solution was evaporated at 380°C in a gas-phase tubular reactor and passed with nitrogen at 450°C over a catalyst ($\text{TiO}_2 + 2\% \text{K}_2\text{O}$). Condensation and fractional distillation were then carried out. The yield was 45% at a selectivity of 70%.

40

45